Two-Way Coupling Between 1-D Blood Flow and 3-D Tissue Perfusion Models

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Abstract. Accurately predicting brain tissue perfusion and infarct volume after an acute ischaemic stroke requires the two-way coupling of perfusion models on multiple scales. We present a method for such two-way coupling of a one-dimensional arterial blood flow model and a three-dimensional tissue perfusion model. The coupling occurs through the pial surface, where the pressure drop between the models is captured using a coupling resistance. The coupled model is used to simulate arterial blood flow and tissue perfusion during an acute ischaemic stroke. Infarct volume is estimated by setting a threshold on the perfusion change. By coupling these two models, we can capture the effect of retrograde flow and its effect on tissue perfusion and infarct volume.

Keywords: Cerebral tissue perfusion · Acute ischaemic stroke · Multi-scale modelling · Infarct volume modelling · Blood flow simulations

1 Introduction

An acute ischaemic stroke (AIS) is caused by the sudden blockage of a cerebral vessel by a thrombus. Every year, millions of people suffer an AIS, resulting in disability and possibly death [5]. The sudden loss of blood flow to tissue, i.e. perfusion, leads to the formation of a cerebral infarct. Understanding how an infarct forms during an AIS can help medical decision making and treatment development. To understand infarct formation, it is necessary to understand how an AIS affects brain tissue perfusion. Unfortunately, predicting brain tissue perfusion is not trivial.

One particular problem is the range of scale of the cerebral vasculature. The diameter of blood vessels ranges from micrometers in the capillaries to millimeters in the large systemic arteries. There are billions of vessels in the microcirculation. Solving the Navier-Stokes (NS) equations for the entire vascular

system is currently not feasible. As a result, approximations have to be made to solve parts of the vascular system using simplified equations. One-dimensional approximations of the NS equations accurately capture blood flow for the large vessels [1,18,19,23]. The microcirculation can be described as a three-dimensional porous medium [6,8,10,13].

There are multiple phenomena where effects on the small scale have an effect on the large scale, and vice-versa. For instance, a growing infarct affects the flow of blood by the death of capillary pericytes, leading to vessel constriction [7]. In addition, retrograde blood flow beyond the thrombus is often observed [2,21]. Capturing these phenomena and their effect on arterial blood flow and tissue perfusion requires a fully coupled model that captures blood flow on multiple scales. Accurately predicting infarct volume after an AIS therefore requires two-way coupling of models of blood flow models describing arterial blood flow and cerebral tissue perfusion.

Here, we present a method for the two-way coupling between a one-dimensional blood flow model to a three-dimensional tissue perfusion model. The coupling occurs through the pial surface where the pressure drop between the models is captured using a coupling resistance. First, a test model of the brain is used to illustrate the models, the coupling algorithm, and show the accuracy of the solutions. Then, the coupled model is used to simulate arterial blood flow and cerebral tissue perfusion during an AIS. The change in tissue perfusion and infarct volume are quantified and compared to the uncoupled case.

2 Methods

The main focus of this work is the coupling of a one-dimensional blood flow (1-D BF) and a three-dimensional tissue perfusion model (3-D perfusion). The 1-D BF and 3-D perfusion models in this work are briefly described for completeness. We refer to our previous work for a more detailed description of the individual models [10,15].

2.1 One-Dimensional Blood Flow Model

Blood vessels are modelled as thin elastic tubes and blood as an in-compressible viscous fluid. Every vessel segment is modelled as a pressure-dependent resistance. The vessels are discretised to a minimum of three nodes, i.e. two terminal and one internal node, and to a maximum resolution of 2.5 mm along the length of the vessel.

The pressure in the network is calculated by solving the mass-balance equations given by

$$\sum_j G_{ij}\,(P_i - P_j) = S_i \tag{1}$$

with P_i the pressure at node i, G_{ij} the conductance, i.e. inverse of resistance, between nodes i and j, and S_i a source term for every node i. The conductance

of a segment is given by $G = \frac{\pi R^4}{2(\zeta+2)\mu L}$, where R is the mean segment radius, L is the segment length, μ is the dynamic viscosity, and ζ is a constant related to the velocity profile, with 2 representing a parabolic profile, i.e. laminar flow, and 9 representing a flatter profile [20]. The larger constant is the result of a blunt velocity profile in the vessel [3]. We use the constant of a blunt profile, $\zeta = 9$.

The resulting system can be written as

$$\mathbf{G}\vec{P} = \begin{bmatrix} \sum G_{1j} & -G_{12} & \cdots & -G_{1N} \\ -G_{21} & \sum G_{2j} & \cdots & -G_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ -G_{N1} & \cdots & \cdots & \sum G_{Nj} \end{bmatrix} \begin{bmatrix} P_i \\ \vdots \\ \vdots \\ P_N \end{bmatrix} = \begin{bmatrix} S_i \\ \vdots \\ \vdots \\ S_N \end{bmatrix} = \vec{S} \tag{2}$$

The pressure-area relationship of a vessel is given by [14]

$$P = P_0 + \frac{\sqrt{\pi}Eh}{A_0\,(1-\nu^2)} \left(\sqrt{A} - \sqrt{A_0} \right) \tag{3}$$

The volumetric flow rate in a segment, Q_{ij}, is calculated by

$$Q_{ij} = (P_i - P_j)\, G_{ij} \tag{4}$$

The resulting system is solved iteratively until

$$\varepsilon_P = \frac{\left| \vec{P_i} - \vec{P_{i-\mathbf{1}}} \right|}{\left| \vec{P_i} \right|} < 10^{-12} \tag{5}$$

with $\vec{P_i}$ and $\vec{P_{i-\mathbf{1}}}$ being the pressure vectors during the i^{th} and $(i-1)^{th}$ iterations, respectively.

2.2 Three-Dimensional Tissue Perfusion Model

Tissue perfusion is simulated using a multi-compartmental porous medium approach [10]. Three compartments are used to simulate blood flow through the arterioles, capillaries and venules. The compartments are located at the same spatial location and are coupled locally.

The equations describing flow through the three compartments are given by

$$\begin{aligned} \nabla \cdot (\mathbf{K_a} \nabla p_a) - \beta_{ac}(p_a - p_c) &= 0 \\ \nabla \cdot (\mathbf{K_c} \nabla p_c) + \beta_{ac}(p_a - p_c) - \beta_{cv}(p_c - p_v) &= 0 \\ \nabla \cdot (\mathbf{K_v} \nabla p_v) + \beta_{cv}(p_c - p_v) &= 0 \end{aligned} \tag{6}$$

where p_a, p_c, p_v are the pressure corresponding to the arterial, capillary and venule compartment, $\mathbf{K_a}$, $\mathbf{K_c}$, and $\mathbf{K_v}$ are the permeability tensors of the respective compartment, and β_{cv}, and β_{cv} are the coupling coefficients between the arterial-capillary, capillary-venule compartments respectively. The brain is

divided into white and grey matter regions with different coupling coefficients. The model parameters are optimised to achieve pre-set perfusion targets with a total cerebral perfusion of 600 mL/min. For the full derivation, solution method, and motivation, we refer to [10].

Tissue perfusion, in units of mL/min/100mL, is calculated as

$$F = 6000\beta_{ac}(p_a - p_c) \tag{7}$$

where 6000 is a unit conversion factor, the product of 60 seconds and 100 mL. Tissue perfusion drops during a stroke, the perfusion change is defined as

$$F^{\Delta} = \frac{F^{Stroke} - F^{Healthy}}{F^{Healthy}} 100\% \tag{8}$$

An infarct can be determined by setting a threshold for the change in perfusion, a value of -70% is used in this paper [4].

2.3 Two-way Coupling Between Blood Flow And Tissue Perfusion Models

We assume that between the outlets of the 1-D BF model and the 3-D perfusion model, vessels exist that are not included in either of the models and that result in a pressure drop. Furthermore, we assume that each outlet of the 1-D model has its own perfusion territory on the pial surface. These regions are determined by a mapping algorithm, as described previously as part of our previous work [15]. During a baseline simulation, i.e. healthy scenario, the surface pressure of the 3-D perfusion model is assumed to be $p_{surface}$. Setting the pressure at the surface to $p_{surface}$ closes the 3-D perfusion model. The flow rate at the surface for each perfusion territory Q_i can then be calculated by integrating the velocity, (for example, $u_a = K_a \nabla p_a$)", normal to the surface over the area. The coupling resistance between both models can be calculated as

$$R_i = \frac{P_i - P_{surface}}{Q_i} \tag{9}$$

where i corresponds to the outlet nodes of the 1-D BF model. The coupling resistance is added to each outlet of the 1-D BF model with the outlet pressure set to $p_{surface}$. The 1-D BF model is solved and the outlet resistance updated until a relative tolerance of 10^{-9} is reached. To ensure convergence of the model, the coupling resistance is first calculated using the venous pressure. If the pressure at the outlets is less than $p_{surface}$, the inlet pressure is increased with the difference until the lowest outlet pressure is larger than $p_{surface}$. Finally, the coupling resistance is calculated using equation 9.

During a stroke, the assumption of a uniform surface pressure is lifted. The coupling problem becomes finding the surface pressures such that the two models agree on the volumetric flow rate at each outlet. This optimisation problem is solved using a Newton-Krylov solver minimising the difference in volumetric flow rate between the models to a relative tolerance less than 10^{-9}. A uniform surface

pressure, i.e. $p_{surface}$ is used as an initial guess for the solver. The optimisation algorithm requires on the order of 3 iterations before convergence. The total run time is around 2.5 hours on a AMD Ryzen 7 3700x 8-core processor with 80 GB of RAM. The main computational cost is running the 3-D perfusion model to obtain an estimate of the Jacobian. The model parameters used in the simulations are listed in Table 1.

2.4 Test Model

A test model is created by combining a bifurcating tree with a cube. In the arterial compartment, four sides of the cube are coupled to the bifurcating tree, the top and bottom sides set as no flow boundaries. In the capillary compartment, all sides are set as no flow boundaries. In the venule compartment, the four sides coupled to the bifurcating tree are set to venous pressure, the top and bottom sides as set as no flow boundaries. The cube is divided into white and grey matter regions with different coupling coefficients. A symmetric bifurcating tree is generated using Murray's law, given by $R_0^3 = 2R_1^3$, starting from an initial vessel with a length of 200 mm, a radius of 10 mm and a Young's modules of 0.4 MPa. Daughter vessels have a Young's modules of 1.6 MPa, similar to a cerebral arteries. The model parameters used in the simulations are listed in Table 1. The parameters are optimised to obtain a a pre-set perfusion in the healthy case of 600 mL/min according to [10]. A stroke is simulated by occluding one of the first generation vessels. The dimensions of the cube are 100 mm per edge, the inner white matter region has dimensions of 50 mm per edge with a cut-out cube of 25 mm per edge.

Table 1: Model parameters, superscripts G and W indicate values corresponding to grey and white matter.

	Cube	Human Brain	
Parameter	Value	Value	Unit
p_{in}	12500	12500	Pa
p_{venous}	0	0	Pa
$p_{surface}$	9000	8000	Pa
ν	0.5	0.5	-
μ	3.5	3.5	mPa
ζ	9	9	-
k_a	7.61×10^{-3}	1.987×10^{-3}	mm^3s/g
k_c [6]	4.28×10^{-7}	4.28×10^{-7}	mm^3s/g
k_v	1.52×10^{-2}	3.974×10^{-3}	mm^3s/g
β_{ac}^G	1.699×10^{-6}	1.624×10^{-6}	Pa/s
β_{cv}^G	5.947×10^{-6}	5.683×10^{-6}	Pa/s
β^G/β^W	2.61	2.58	-

3 Results

3.1 Test Model

Figure 1 shows the test model designed to illustrate the models and the coupling algorithm. A section is removed to show the inner parts of the brain. The blood flow model is a symmetric bifurcating tree with four outlets and one inlet, Figure 1a shows the pressure when a thrombus is occluding one of the vessels. Figure 1b shows the brain mesh used in this example. The brain consists of white matter and grey matter, which differ in their coupling coefficient, Figure 1c shows the coupling coefficients for white and grey matter regions. Figure 1d, Figure 1e, and Figure 1f show the pressure in the arteriole, capillary, and venule compartments respectively during an occlusion. The volumetric flow rate through the top and the bottom surfaces is zero, the other four sides are coupled to the bifurcating tree shown in Figure 1a. Tissue perfusion is calculated using equation 7. Figure 1g shows tissue perfusion during baseline while Figure 1h shows tissue perfusion during an occlusion. The resulting perfusion change is shown in Figure 1i.

3.2 Coupled Brain Model

The coupled model consists of a 1-D BF model and a 3-D perfusion model, as shown in Figure 2. Figure 2a and Figure 2b show the 1-D BF model and the 3-D perfusion model respectively. The two models are coupled through the pial surface, Figure 2c, a coupling resistance captures the pressure drop caused by absent vessels. Figure 2d shows the pressure during a baseline simulation; Figure 2e shows the resulting tissue perfusion during this baseline simulation.

3.3 Modelling Acute Ischaemic Stroke

An AIS can be simulated by occluding one of the major cerebral vessels. The occlusion in the simulations presented here is located in the right middle cerebral artery (MCA). Figure 3 shows the difference between the uncoupled and coupled models during an AIS. Figures 3a and 3b show the pressure in the 1-D BF model, while Figures 3c and Figure 3d show tissue perfusion during during an occlusion of the right MCA for the uncoupled and coupled models respectively. Figure 3e and Figure 3f show the change in tissue perfusion during the same occlusion. If the models are not coupled, the predicted volumetric flow rate and pressure at the boundary regions downstream of the occlusion predicted by the 1-D BF model are zero and venous pressure respectively. Simulating brain tissue perfusion with these values results in the worst-case scenario. Simulation brain tissue perfusion with two-way coupling results in smaller predicted infarct volumes. Table 2 lists tissue perfusion and infarct volumes values per simulation.

4 Discussion

Coupling arterial blood flow and tissue perfusion models is not trivial. One difficulty occurs due to the difference of the mathematical formulation of the

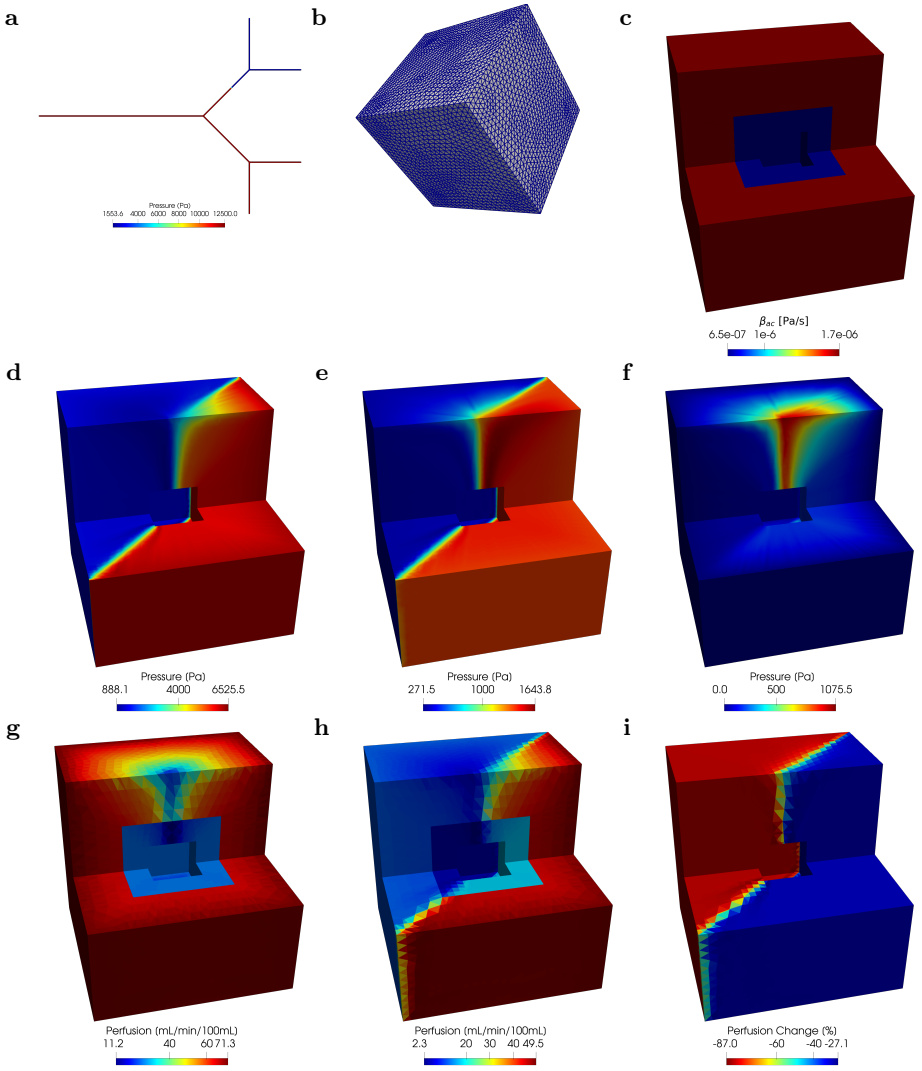

Fig. 1: (a) The arterial blood flow model consists of a symmetric bifurcating tree. Shown is the pressure during an occlusion of the first daughter vessel. (b) The brain mesh used in this example. (c) The permeability coefficients of the perfusion model. White and grey matter regions have different values. (d, e, f) Pressure during an occlusion in the arteriole, capillary and venule compartments respectively. (g) Healthy tissue perfusion. (h) Tissue perfusion during an occlusion. (i) Perfusion change as a result of an occlusion.

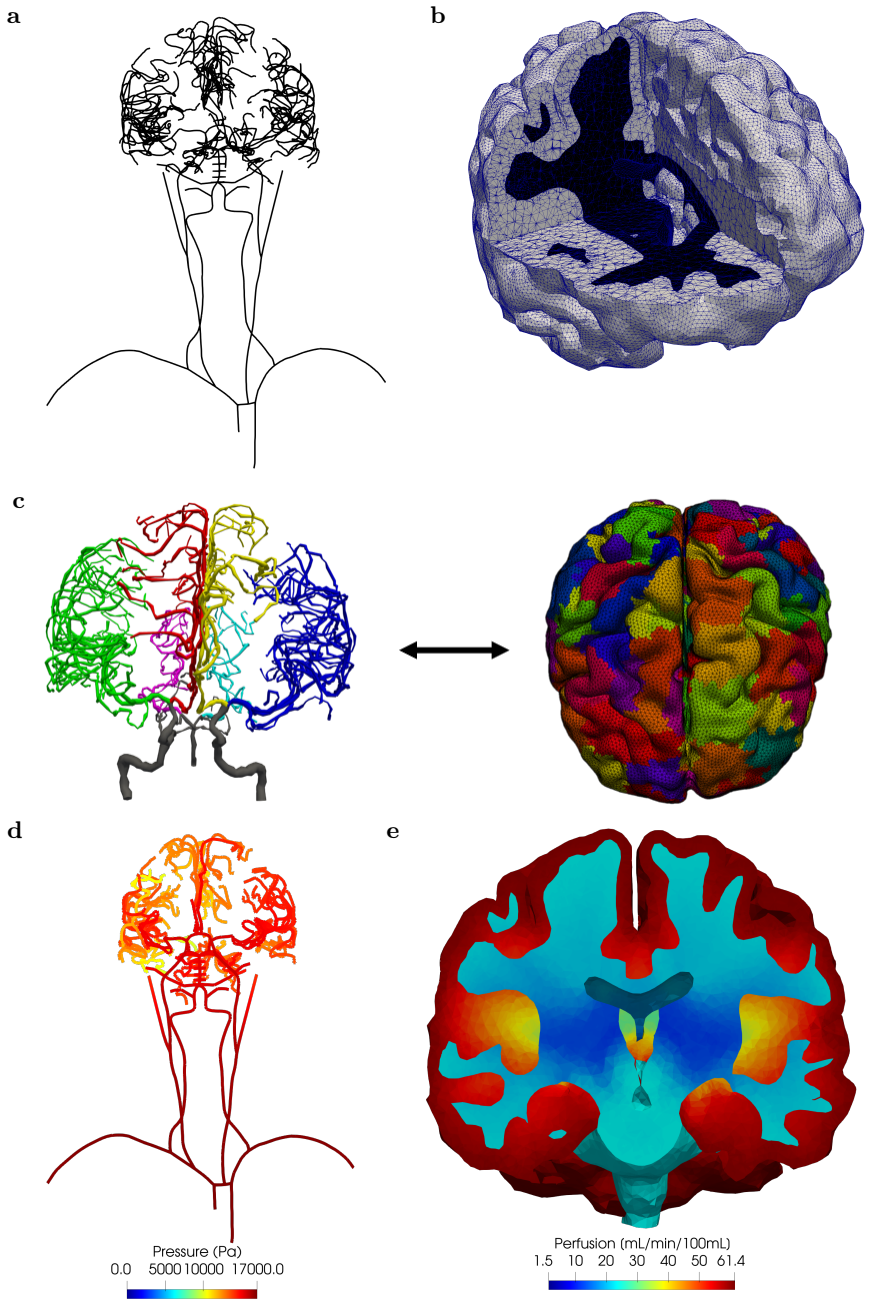

Fig. 2: (a) The 1-D BF model. (b) The mesh used in the 3-D perfusion model. Shown are the white and grey matter regions. A region is cut out to show the inner regions. (c) The coupling method between the models. Each outlet of the 1-D BF model is connected to a surface region on the boundary of the brain mesh. (d) Pressure in the 1-D BF model during baseline. (e) Tissue perfusion in the 3-D perfusion model during baseline.

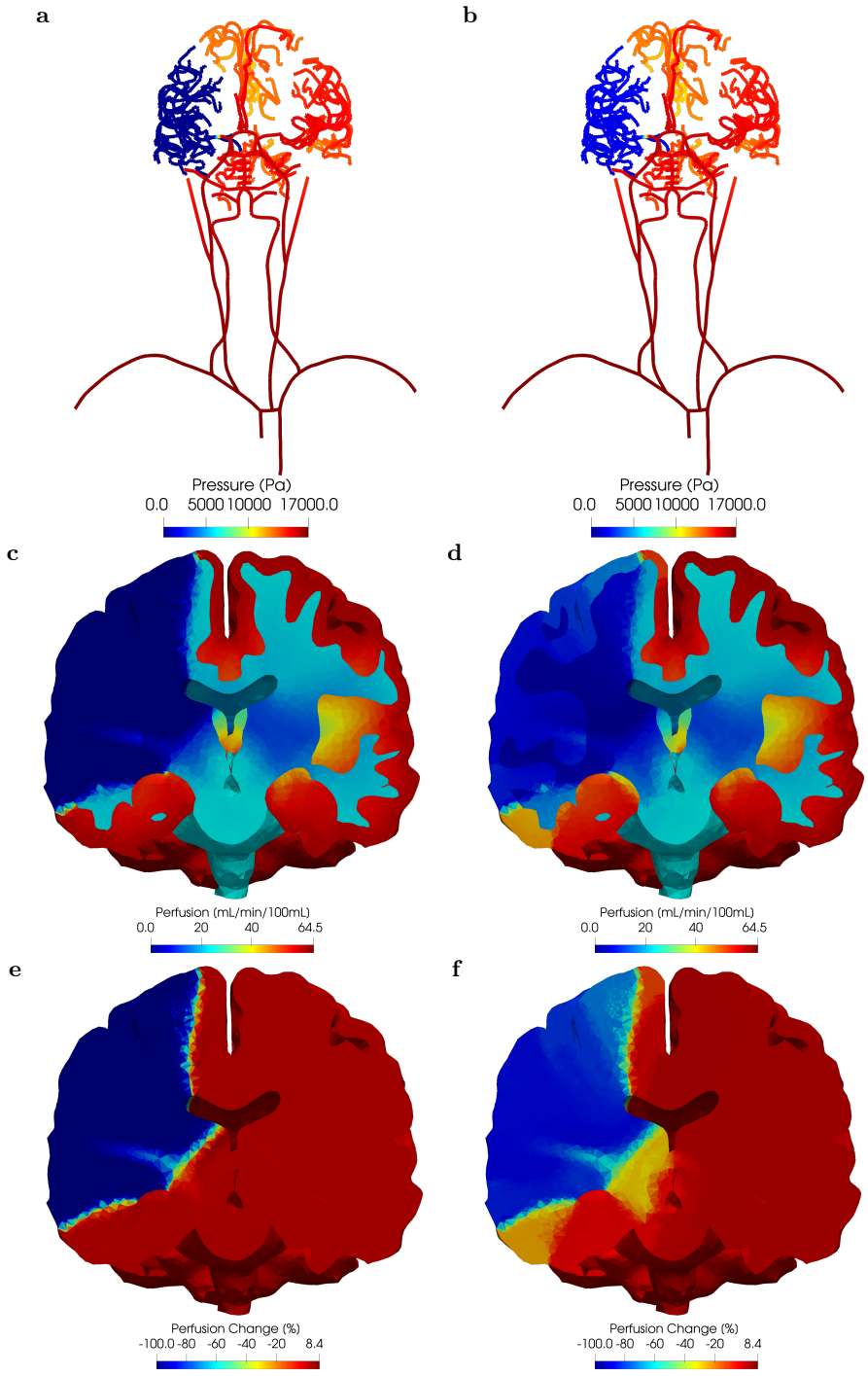

Fig. 3: Comparison between uncoupled and coupled models during an occlusion. Front view of the brain, the brain is sliced to reveal the inner parts. (a) Pressure in the uncoupled and coupled 1-D BF model respectively. (c, d) Tissue perfusion in the uncoupled and coupled 3-D perfusion model respectively. (e f) Tissue perfusion change in the uncoupled and coupled 3-D perfusion model respectively.

Table 2: Tissue perfusion and infarct volume values.

	Tissue Perfusion [mL/min/100mL]			Infarct Volume [mL]		
Simulation	Healthy	Uncoupled	Coupled	Healthy	Uncoupled	Coupled
Grey Matter	55.67	43.47	45.53	0.0	189.4	162.4
White Matter	20.62	15.47	16.36	0.0	120.0	99.2
Total	43.16	33.47	35.12	0.0	309.4	261.5

two models. The one-dimensional arterial blood flow model describes pressure and flow rates as discrete values in a single point, while the three-dimensional tissue model uses volume averages over the surface. This difficulty is resolved in our model by the use of a coupling surface at the cerebral cortex, or pial surface. An alternative is the use of a volume source term, such as Peyrounette et al. have done [17]. The human brain is perfused through the pial surface by the penetrating arterioles [9]. The use of a coupling surface, i.e surface source terms, is therefore a valid alternative to volume source terms. In addition, this approach also simplifies the coupling. The surface pressure of the human brain is not known in detail and is assumed in this paper to be 8000 Pa (60 mmHg). The perfusion model parameters are optimised to achieve a pre-set total perfusion of 600 mL/min during the baseline simulation regardless of surface pressure.

Another difficulty arises due to the unavailability of data of the entire cerebral vasculature for a single patient. Between the two models, there is a lack of information by the absence of the pial surface vessels. We solve this problem by calculating a coupling resistance between the models. The resistance captures the effect of the missing vessels. Another approach would be to explicitly generate a bifurcating tree with equivalent resistance [12,16]. However, the outlets of these trees would also need to be explicitly coupled to the tissue model. The coupling resistances found depend on the value of assumed surface pressure, a higher pressure leads to a smaller value and therefore less resistance. The total resistance in the system sets the amount of flow while the relative fraction at each outlet determines the volumetric flow rate at that outlet.

The velocity profile in the large vessels is not parabolic but rather blunt [20]. Models of the large vessels account for this by increasing the resistance. In the microcirculation, a laminar velocity profile is often assumed. In this paper, the 1-D BF model uses the parameter of a blunt profile to calculate the pressure. This choice results in a larger pressure drop in the arteries. The blunt profile does not hold for the entire vasculature and decreases towards a parabolic profile, i.e. laminar flow in the microcirculation. However, it is not clear how this parameter changes and is therefore kept constant in this paper. The assumed pial surface pressure in the healthy scenario can be incompatible with the assumed velocity profile. To still achieve convergence, the inlet pressure is increased until the lowest pressure at an outlet matches the assumed surface pressure. For a laminar velocity profile, the inlet pressure does not need to be increased. It is worthwhile

to note that the tissue perfusion and infarct volume values are not affected by the choice of velocity profile parameter.

Figure 1 shows a simple example of a bifurcating tree representing the arterial vasculature and a cube representing the brain. The perfusion parameters are optimised to achieve a total perfusion of 600 mL/min during the baseline simulation. An occlusion is simulated by occluding one of the branches. The un-occluded branch then provides all blood flow to the downstream tissue. However, it is unable to perfuse the entire volume at the same level. As a result, the entire volume is perfused at a lower level with the furthest regions dropping the most. The infarct volume in this case would be half the volume, depending on the chosen threshold. Note that tissue perfusion does not drop to zero anywhere in the volume. The surface pressure in the baseline simulation is chosen to be 9000 Pa as the pressure drop in the bifurcating tree is much smaller than for the human brain. Choosing a different value for the surface pressure will change the coupling resistances as a smaller pressure drop between the models means less resistance for the same volumetric flow rates. During an occlusion, the surface pressure drops as the volumetric flow rate increases.

Figure 2a and 2b shows the 1-D BF model and tissue perfusion model applied to a human cerebral vasculature and brain respectively. The outlets of the 1-D BF model are coupled to surface regions on the surface of the brain, as shown in Figure 2c, the coupling resistances are not shown. By assuming a uniform surface pressure at the surface of the 3-D perfusion model, the volumetric flow rates can be calculated and used to determine the coupling resistances. Figures 2d and 2e show the resulting baseline simulation for the 1-D BF and 3-D perfusion models respectively. The baseline simulations are able to achieve realistic values for tissue perfusion, as shown in Table 2.

Figure 3 shows a comparison between the uncoupled and coupled versions of the model. Coupling the two models provides a different estimate of the pressure and flow rates at the pial surface than the uncoupled model. The perfusion change, Figures 3e and 3f, show that tissue perfusion drops less in the coupled model. The surface pressure in the coupled model is larger than in the uncoupled model. The surface pressure during an occlusion is not set to a certain value in the coupled model, but is instead the solution of a root finding algorithm. This provides a more accurate solution of the surface pressure during an occlusion. In the coupled model, the regions surrounding the infarcted region are perfused less as a result of retrograde flow. Table 2 lists the difference in mean tissue perfusion and infarct volumes for the healthy, uncoupled and coupled simulations. The coupled model results in a lower infarct volume at the chosen threshold.

The simulations presented in this paper represent a patient with a complete occlusion of the right MCA without any collateral vessels. These vessels provide flow through alternative pathways and maintain perfusion [11,22]. In addition, the effect of tissue death on blood flow is neglected. These effects are outside the scope of this paper. We are planning to investigate the neglected features in future. The simulations presented here therefore represent a worst-case scenario. Two-way coupling is necessary to provide better estimates of infarct volume,

capture the effect of collateral flow, and simulate the growth of the infarct core. Our aim is the creation of a model that can simulate the formation and growth of the infarct volume during an AIS. By coupling these two types of models, we are one step closer to accurately predicting infarct volume and location.

5 Conclusion

Accurately predicting infarct volume after an AIS requires two-way coupling of models describing arterial blood flow and tissue perfusion. Here, we present a method for the two-way coupling between a one-dimensional arterial blood flow model and a three-dimensional tissue perfusion model. A test model is presented to showcase the models and algorithms. The two-way coupling allows for feedback between the models, thereby capturing retrograde flow and leading to a smaller estimate of infarct volumes.

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7 Conflicts of Interest

The authors declare no conflict of interest

8 Authors' contributions

R.M.P. has developed the coupling algorithm, the 1-D blood flow model and written the manuscript under the supervision of G.Z and A.G.H. T.I.J. has pre-processed the brain mesh, developed the 3-D tissue perfusion model and the optimisation of the model parameters under the supervision of S.J.P. All authors have contributed to the design of the research and revision of the paper.

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